What's new in paediatrics? (Review)

Benjamin Osler is reputed to have stated that he knew that 50% of what he was teaching his students was going to be proven wrong; the only problem was he did not know which 50%!

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Today, nearly one hundred years later, it still behoves all practitioners to emulate Osler's humility with regard to the permanence of their knowledge and insight. New insights with regard to old diseases, newly emerging conditions, new technologies and new treatment possibilities all demand that the most important attribute of a newly qualified medical practitioner is to become a lifelong learner.

In this article I highlight changing insights into old knowledge, emphasise new understanding of common conditions, and discuss some new preventive and promotive strategies.

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Early origins of adult disease

For a long time it has been known that babies who were deprived *in utero* and born small for gestational age have higher long-term health risks, including growth disturbance and a variety of neuro-endocrine problems. Barker and co-workers' epidemiological studies[1] showed that babies born small had a higher risk of obesity, the metabolic syndrome, type II diabetes mellitus, hypertension and coronary vascular disease, particularly if these babies had shown rapid catch-up growth in early childhood. The term 'programming' was introduced to refer to an influence at a critical sensitive period of development resulting in long-term changes in physiology or metabolism.[2] Suggested mechanisms include decreased number of cells, altered organ structure or abnormal setting of endocrine axes and feedback systems.

It was also shown that the intrauterine environment could lead to heritable intergenerational effects, suggesting that programming could have a genetic component. Such modifications of gene function occurring without a change in gene sequence are referred to as epigenetic changes. They are caused by methylation of cytosine-phospho-guanine (CpG) dinucleotides. Where such methylation occurs within gene promoters, it can lead to repression of transcription activation and 'silencing' of associated genes. This particularly applies to the so-called imprinted genes with uniparental mono-allelic expression and to transposons, both of which are transcriptionally regulated by CpG methylation.[3]

Examples of imprinted genes potentially involved in nutritional epigenetic mechanisms include IGF2, leptin and insulin2.[4] There exist specific, critical periods of epigenetic vulnerability during gametogenesis and embryogenesis, but also during late neonatal and early postnatal life.

Mammalian 1-C metabolism is dependent on dietary methyl donors, principally methionine. Epigenetic programming, whereby DNA methylation is related to the environmental concentration of methyl donors, may therefore have nutritional antecedents during intrauterine and early postnatal development. The resulting conformational change in chromatin can permanently alter the genetic risk profile of the individual.

Clinical relevance

The intrauterine environment of the developing fetus has far-reaching consequences for its whole-life health risk profile. Insofar as this can be influenced by antenatal care and nutrition, the health practitioner has a responsibility far greater than just the survival and live birth of the fetus.

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Increasingly, the actual composition and balance of nutrients in early infancy is also linked to nutritional epigenetic programming. The prevailing nutritional environment is thought to influence the developmental state to produce a phenotype most suited to an expected later environment.[5] Therefore, nutritional restriction during gestation is associated with decreased body size at birth, decreased insulin responses to various secretagogues, increased whole-body insulin sensitivity and receptor expression, and selective resistance to inhibition of lipolysis by insulin; effectively, prenatal nutritional deprivation programmes for survival in an expected nutritionally impoverished environment. This compares with the 'thrifty phenotype'[6] vulnerable to increased risk if subsequently exposed to nutritional excess. In humans, some evidence for this sequence is seen in epidemiological studies demonstrating the highest risk for subsequent development of cardiovascular disease in those born small and growing fastest during early infancy.[7] In laboratory animals deprived during gestation, variable effects are seen on subsequent blood pressure measurements, depending on the type of protein or amino acid supplementation of the diet, and also rapid catch-up growth and reduced lifespan from renal disease.[8]

A situation in which the fetus is programmed for thrift, but subsequently exposed to nutritional excess, can be referred to as an environmental mismatch.[5] This is potentially of great significance in developing societies experiencing a rapid socio-economic transition.[9] In keeping with this hypothesis is the observation that developing countries show some of the most rapid increases in the prevalence of obesity globally.

Not only the quantity, but also the type of food exposure in early infancy may have long-lasting effects on growth and weight gain. Studies comparing nutrient intakes and subsequent outcomes between breastfed and formula-fed babies have shown effects attributable to type and quantity of protein exposure.[10] Human milk protein has been found to have a differing effect on lean body mass and fat accretion, and greater nutrient efficiency than infant formula.[11] Biochemical analyses of serum amino acid levels in response to formula protein showed elevation of most of the essential amino acid levels compared with those found in breastmilk-fed babies, generally proportional to the level of protein found in the formula,[12] and also demonstrated a linear relationship between serum branched-chain amino-acid concentration and serum C-peptide responses.[13,14]

Exposure to non-human protein in the highest tertiles of protein intake as a proportion of total energy intake was associated with fastest growth and weight gain.[15] Cow's-milk protein intake was associated with elevated s-IGF1 in a cross-sectional study of 2.5-year-old children and in an interventional study of 8-year-old boys.[16,17] Excess protein intake in the first 2 years leads to increased IGF1 and insulin resistance with subsequent risk of metabolic and cardiovascular disease – the 'early protein' hypothesis.[18]

Clinical relevance

Modern infant formulas have recently been adapted to reduce the protein content. The type and amount of food given to infants may well have a programming effect on subsequent metabolic responses.

Breastfeeding

After a massive decline in breastfeeding from the 1940s up to the early 1970s, when more than 70% of babies in the USA received no breastmilk at all, there is an increasing appreciation that human breastmilk has numerous important long-term protective advantages, even in situations where safe and adequate replacement feeding can be practised.

Given that many new mothers experience significant difficulties with the onset of lactation and do not always have the benefit of helpful advice from experienced women in the household, the availability of lactation consultants must be actively encouraged and welcomed. Lactation support and help from organisations such as *La Lèche* League can also be invaluable. It is certainly not appropriate for doctors to respond to lactation-onset difficulties in their patients by recommending a switch to formula.

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Even for HIV-infected mothers, the risk of HIV transmission through breastmilk must be seen in relation to the risks of not breastfeeding. When replacement feeding is associated with an increasing risk of death from infections and malnutrition rather than from HIV, the cumulative HIV-free survival may not be significantly different between breastfeeding and formula feeding. The infection risk from breastmilk depends on the mother's HIV viral load, her breast health and the infant's gastrointestinal health, with exposure to mixed breastfeeding and formula feeding imposing an additional risk. A rational policy therefore is to ensure that breastmilk is as safe as possible by instituting maternal antiretroviral therapy in late pregnancy and lactation and by adherence to best-practice prevention of mother-to-child transmission of HIV.

The reported protective effects of breastmilk feeding range from developmental and immunological to metabolic advantages.[19-22] These include a positive effect on development seen in randomised feeding studies of preterm babies up to 8 years later, a greater immunological maturation compared with babies receiving formula feeds, and an advantageous metabolic profile with regard to lipid and carbohydrate metabolism.

Breastfeeding impacts on allergy and asthma in a number of ways, including a delayed exposure to foreign dietary antigen; promotion of gastrointestinal maturation and closure to macromolecular absorption; a decrease in the incidence of gastrointestinal infection; and immunomodulatory and anti-inflammatory factors that include beneficial cytokines and growth factors.

Breastmilk feeding is also suggested to help protect against subsequent obesity,[23,24] even though the effect is only moderate.

Breastfed babies have been shown to have a systematically different growth pattern to formula-fed babies. After the first few months of excellent growth, breastfed babies gain weight more slowly than formula-fed babies, although their growth in length is not affected. Consequently, they appear to be relatively thin in the second year of life. This weight-for-length discrepancy lasts until after the age of 2 years, when the growth patterns again converge. This was previously interpreted as indicating a relative energy deficit in the diet of breastfed babies, even though it obviously occurred at an age when babies were already on additional weaning diets. Mothers should be reassured that such growth is normal. The growth of breastfed babies should consequently not be plotted on standard NCHS growth charts, but rather on the new WHO charts (www.who.org/growth).

Clinical relevance

It is currently again recognised that for normal newborn babies breastfeeding is not only the best, but indeed the norm and the only rational and correct choice.

Food for health: The role of functional foods

Functional foods are claimed to cause a positive health effect by containing substances that improve function in some way without necessarily correcting deficiency. These may include macronutrients and micronutrients such as vitamins, trace elements, prebiotics and amino acids. Even though such substances may have considerable potential for biological interaction, the relevant food control legislation requires proof of safety rather than proof of benefit versus risk.[25] Accordingly, advertising does not always have to meet stringent standards of scientific validation for the claimed health benefits.

Not surprisingly, then, that mothers who are faced with a bewildering array of choices of foods and formulas supplemented with prebiotics, probiotics, nucleotides, vitamins and trace elements, minerals and fatty acids may become confused. It is not easy to appreciate that even if a particular benefit can be shown for one substance, e.g. an antidiarrhoeal effect of a specific probiotic, this can not necessarily be generalised with regard to all other substances in that class.

Provided a child is growing normally and receives a balanced diet, the added benefit of supplemented foods is usually not proportional to the additional

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expenditure. One should therefore guard against superfluous broad-spectrum supplementation of healthy children, and overzealous prescription of single items such as vitamin A. Clear evidence has been presented that vitamin A administration as a single supplement is associated with an increasing risk of vertical HIV transmission and subsequent morbidity and mortality.[26]

On the other hand, trace elements and vitamins may take on a pharmacological role during illness. The effects of zinc in diarrhoea exceed those of just correcting deficiency.[27]

Clinical relevance

There is undoubtedly a role for nutrient supplementation in illness and deficiency, but unselected broad-spectrum and multiple food supplements for healthy children are not necessary.

New rotavirus vaccines

Rotavirus gastroenteritis is the commonest cause of infantile gastroenteritis worldwide, accounting for up to 40% of diarrhoea deaths.[28] Prevention of rotavirus diarrhoea has been identified by the WHO and the Global Alliance for Vaccines and Immunizations as one of the priorities in developing countries. The first rotavirus vaccine had to be withdrawn after a higher than expected rate of intussusception in a few vaccinated babies. Consequently, all subsequent candidate vaccines were subjected to extremely large and detailed safety and efficacy trials. The new vaccines are safe. Even after several million doses, there have been no excess cases of intussusception reported in post-licensing surveillance. Two different live vaccines are available – a highly attenuated human rotavirus strain (Rotarix) and a bovine-human reassortant pentavalent strain (Rotateq).

It is important to note that surface infections such as those caused by the rotavirus require mucosal invasion before vaccine-induced immunity can recognise the invader and protect the individual. Accordingly, vaccination does not fully prevent infection or all disease, but both vaccines have been shown to be highly effective in preventing severe disease, hospitalisation and death[28] due to prevalent serotypes in the developed world.

The problem of diarrhoea in the developing world is obviously strongly linked to environmental factors and nutrition, and is often associated with mixed infection. In addition, a greater variety of rotavirus strains cause disease than in the developed world,[29] and it is not yet known whether emerging strains might replace the usual disease-producing strains. Under such circumstances the effect of immunisation might not be so obviously noticeable, and is also dependent on local programme delivery factors such as cold-chain maintenance and vaccination uptake.

Clinical relevance

Nevertheless, rotavirus immunisation is strongly advised, both at the individual level of private practice and in the public sector.

Immune-mediated disease and inflammation

There has been an increase in the number of immune-mediated diseases during the second half of the 20th century, including type I diabetes mellitus, coeliac disease and inflammatory bowel disorders.[30] For diabetes mellitus, at least, this may reflect a younger age of onset in genetically predisposed individuals[31] and thus 'unmasking' of auto-aggressive damage by environmental factors, including early nutrition (including failure to breastfeed) and common infections. Similar observations have been made for asthma and allergic disorders.

The common pathogenetic postulates concern early environmental influences on the maturation of local and systemic immune responses and consequently on the propensity to inflammation in response to environmental antigen exposure in genetically predisposed individuals. Intriguingly, recent literature introduces the concept of critical time windows for the development of oral tolerance to nutrients such as gliadin in the development of coeliac disease. It is not yet known whether similar factors can be shown in other immune-mediated diseases.

Clinical relevance

Apart from progress in the development and application of new treatment modalities, the challenge to clinicians is to identify the risk factors involved in the epidemiological changes to the prevalence of immune-mediated diseases and to help to roll back the rising tide.

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In a nutshell

- New insights show that intrauterine and early infant nutrition may induce genetic changes, and that immune-mediated chronic diseases may have their antecedents in infancy.
- The overarching challenge of paediatrics is to keep healthy children healthy.
- It is incumbent on doctors working with children and their families to be cognisant of epidemiological developments in order to be able to counsel families effectively and appropriately.
- The intrauterine environment could lead to heritable intergenerational effects, suggesting that programming could have a genetic component.
- Not only the quantity, but also the type of food exposure in early infancy may have long-lasting effects on growth and weight gain.
- Modern infant formulas have recently been adapted to reduce the protein content. The type and amount of food given to infants may well have a programming effect on subsequent metabolic responses.
- It is currently again recognised that for normal newborn babies breastfeeding is not only the best, but indeed the norm and the only rational and correct choice.
- There is undoubtedly a role for nutrient supplementation in illness and deficiency, but unselected broad-spectrum and multiple food supplements for healthy children are not necessary.
- Rotavirus immunisation is strongly advised, both at the individual level of private practice and in the public sector.